REMARKS

Claims 1-37, 77, 83-94, 97-108, 119, 121, and 123 are pending in the application. No claims are amended in the present reply. Claims 1-37, 77, 84-87, 93, 94, 97 and 101-108 are withdrawn. Claims 38-76, 78-82, 96, 109-118, 120, 122, and 124-130 were previously cancelled. The Examiner is requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 103 – *HERMAN & SLAVIN-CHIORINI*

Claims 83, 88-92, 98-100, 119, and 121-123 stand rejected under 35 U.S.C. § 102(e) as allegedly unpatentable over Herman (U.S. Pub. No. 2005/0069549, published March 31, 2005, filed January 14, 2003; cited in the PTO 892 form of 11/7/2006; hereinafter "*Herman*") in view of Slavin-Chiorini et al. (Int. J. Can. 53:97-103(1993); hereinafter "*Slavin-Chiorini*"). This rejection is respectfully traversed.

In the Response to Arguments on page 5 of the Office Action dated June 1, 2010, the Examiner stresses that the antigenic units and targeting units can be antibody derived. This is of course not incorrect – Applicants' prior response pointed to the fact that functionality as an antibody is not at all an aim of the present invention. The Examiner also challenges the view that *Herman* does not address production of antibody based molecules comprising two monomer units encoded by the same nucleic acid. However, Applicants can support their view by pointing out that *Herman's* antibody molecules must be at least bispecific, that is, they have to bind at least two different antigens. Finally, the Examiner has argued against Applicants' finding that combination between *Herman* and *Slavin-Chiorini* would be avoided when aiming at producing a vaccine, because *Slavin-Chiorini* provides for an increase in plasma clearance.

Applicants wish to draw the Examiner's attention to the fact that the combination of *Herman* and *Slavin-Chiorini* cannot result in the claimed invention. For this purpose, it is relevant to consider the features that characterize the claimed nucleic acid molecules:

1. The nucleic acid encodes a monomer which can form a homodimer.
2. The encoded monomer comprises a dimerization motif consisting of an Ig hinge region and a Cγ3 domain.
3. The encoded monomer is, when forming a homodimer, connected to an identical monomer via disulfide bridges between the Ig hinge regions and hydrophobic interactions between the Cγ3 domains in the two monomers.
4. The nucleic acid does not encode a CH2 domain.
5. The nucleic acid encodes an antigenic unit and a targeting unit.
6. The antigenic unit and the targeting units are separated by the dimerization motif in the encoded monomer.

The Examiner appears to agree that *Herman* does not disclose any DNA constructs having this combination of features, and in particular that the feature of lacking a CH2 domain is a missing feature. However, if *Herman* can be shown to lack more of the above features, then the combination with *Slavin-Chiorini* will not provide the claimed invention and hence cannot render the claims obvious.

The passages cited by the Examiner fail to provide a single indication of an antibody construct where a monomer (which can form a homodimer as stated above) includes a targeting unit and an antigenic unit separated by a Cγ3 domain and an Ig hinge region. On the contrary,

Herman appears to concentrate on multispecific ligands where the different binding affinities in the multi-specific ligands are confined to different chains of the antibody. Accordingly, Applicants respectfully request the Examiner to point out exactly where the *Herman* document provides a direct and unambiguous disclosure of a monomer having targeting units and antigenic units in different termini relative to a dimerization motif, as defined in the present invention. Without such a direct an unambiguous disclosure, *Herman* cannot teach the features of the present claims, even if a skilled artisan were to somehow "extract" the lack of a CH2 domain.

Another important issue is the lack of an apparent reason to combine *Herman* and *Slavin-Chiorini* in a manner that would recreate Applicants' claims. These two documents disclose different technologies that would not lead a skilled artisan to combine them in the fashion alleged in the rejection. *Herman* deals with immunotherapy, and the technology taught therein is essentially a version of the so-called "magic bullet" – an effector moiety is brought into contact with its target via a targeting antibody. In such a technology, a prolonged serum half-life is desired – as pointed out below, considerations concerning half-life are not "irrelevant" as held by the Examiner and a prolonged serum half-life is actually indicated as desirable in *Herman*.

In contrast to this, *Slavin-Chiorini* relates to immune-diagnosis. The solution of removing the CH2 domain provided by *Slavin-Chiorini* is the consequence of undesired side effects induced by using radiolabeled antibodies or antibody fragments in diagnosis; a too prolonged presence of the radiolabeled antibody is in itself pathogenic due to radiation. Further, a prolonged presence of a foreign antibody has the consequence that the antibody acts as an antigen and elicits a HAMA (Human Anti-Mouse Antibody) response. Both of these side-effects, according to *Slavin-Chiorini*, can be diminished by lowering the plasma half-life of the antibodies used by increasing their plasma clearance (i.e., lowering the plasma half-life).

However, since *Herman* deals with immunotherapy, the skilled person would not aim at lowering serum half-life – on the contrary, *Herman* specifically mentions in several locations that it is desirable that half-life may be increased; *cf.* the following disclosures in *Herman*, where half-life of antibodies is discussed:

> [0069]: "...(which Fc if it includes the CH3 is preferably mutated to preclude its binding and/or increase its half life as is known in the art see U.S. Pat. No. 6,121,022)..."
>
> [0104]: (last sentence) "...Methods of prolonging the half-life of antibodies, producing bispecifics, scfvs and dsFvs and altering Fc effector function are well known and noteworthy references include U.S. Pat. No. 6,277,375, U.S. Pat. No. 5,869,046..."
>
> [0167]: "...The invention contemplates a variety of different size multifunctional ligands (MRU, single domain, scFv, Fab, minibodies, $F(ab)_2$, $F(ab')_2$, substantially whole antibodies etc. and known or obvious multimers thereof referenced herein and in the referenced literature) that are most suitable (eg. for small enough or, for example, having longest half life in circulation) for particular modes of administration to the extent that this is a limitation (eg. size, where drainage into the lymphatic system is sought to be increased or optimized)..."
>
> [0338]: "...For example, the carbohydrate moiety can be used to attach polyethylene glycol in order to extend the half-life of an intact antibody, or antigen-binding fragment thereof, in blood, lymph, or other extracellular fluids..."
>
> [0428]: "...U.S. Pat. No. 5,055,289 Interferon antibody therapeutic compositions having an extended serum half-life..."
>
> (emphasis added).

In fact, Applicants cannot find as much as one single indication in *Herman* where it is stated or hinted that the multi-specific ligands therein should be modified to exhibit a decreased half-life – on the contrary, all suggestions point to prolongation of half-life. This is in accordance with the fact that *Herman's* multi-specific binding agents are therapeutic.

Finally, with respect to the issue of an HAMA response, which is discussed in *Slavin-Chiorini* and relied on by the Examiner, Applicants first of all note that such a response is only

relevant if the antibody administered is murine and the antibody is administered to a human; it goes without saying that a HAMA will not be induced by a multispecific ligand which is not derived from a murine molecule or which does not include sufficient murine material to induce a HAMA. The multispecific ligands taught in *Herman* are highly artificial molecules and it is difficult to see that there is any specific disclosure of a DNA fragment encoding a molecule having the features recited in the present claims (still disregarding the CH2 domain's presence or not) and being a molecule which could induce a HAMA response – induction of a HAMA response does require that the administered molecule can induce antibodies that bind to a murine antibody (this is implicit in the expression "human anti-mouse antibody response"). So, when it is alleged in the rejection that the skilled person would be motivated to combine *Herman* and *Slavin-Chiorini* to arrive at the claimed invention, this presupposes that a HAMA response could at all be induced by a construct disclosed in *Herman* – and this has not been demonstrated by the Examiner. In *Slavin-Chiorini*, a HAMA is a true problem, because the antibody used is a murine monoclonal antibody which is immunogenic in humans.

It should also be noted that a HAMA response is not a problem in the present invention. If a protein encoded by the claimed nucleic acid molecule should be capable of inducing a HAMA response, this is at worst irrelevant, but since any induction of immunity against the encoded molecule is desirable, induction of a HAMA response could even be beneficial.

Accompanying the present reply is an affidavit from Prof. Sally Ward of the Southwestern Medical Center to support the above referenced scientific points. In particular, the affidavit supports the fact that *Herman* consistently refers to prolonged serum half-life as desirable and nowhere mentions a reduced serum half-life. Thus, a skilled person would not turn to *Slavin-Chiorini* in order to modify the teachings in *Herman*.

The present claims are therefore not obvious over *Herman* and *Slavin-Chiorini* as there is no apparent reason to combine and modify these documents in a manner that would recreate Applicants' claims, as required by *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 418, 82 USPQ2d 1385, 1396 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue).

Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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